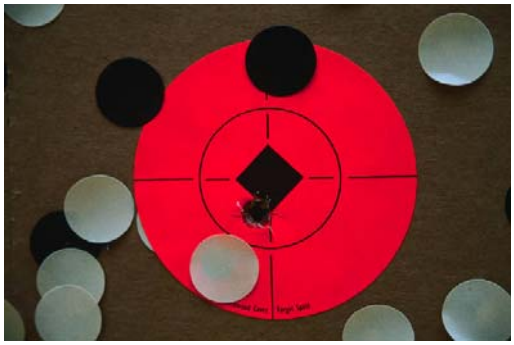
Quarterly Surveillance Report
July 2007
Special Supplement

Cancer Cluster Investigations

Montanans are aware that cancer is becoming more common and many are concerned that environmental hazards contribute to the risk of cancer or other health problems in their communities. The Montana Department of Public Health and Human Services (DPHHS) receives inquiries and reports about potential cancer clusters every year. DPHHS has adopted a standardized protocol to ensure that each report is adequately addressed.[1] The protocol is based on a model developed by the Centers for Disease Control and Prevention.[2]

A cancer cluster is an **excess occurrence** of a single type of cancer (**case definition**) within a specified **time period** and within a defined **population at risk**, typically described by geography or some other common factor. Additional evidence for a potential cluster is cancer in a segment of the population not usually affected by that type of cancer.



The State of Montana's Cancer Cluster Investigation Protocol

Coordination: Each inquiry or report is referred to the Epidemiologist in the Cancer Control Section of DPHHS. The Epidemiologist contacts the local health jurisdiction to inform them of the report and determine who should respond.

Verification: If the DPHHS is designated to respond, the Epidemiologist creates a case definition and gathers all available information on the cases that prompted the call, including time period, location, and suspected environmental hazards, if any. The Epidemiologist verifies the reported cases in the Montana Central Tumor Registry and looks for more cases that fit the case definition. Once all cases are identified, the Epidemiologist calculates incidence rates in the community and in the state as a whole to determine whether there is an unusually high incidence in the community.

Case Definition

Cancer is a general term for cells that grow out of control, no longer perform their

[1] http://www.dphhs.mt.gov/epht/investigationprotocol.pdf
[2] http://www.cdc.gov/nceh/clusters

usual functions, and invade other tissues. Cancer as a category of disease is common: one in three residents of the US will develop cancer in his or her lifetime. Cancers are classified by site (part of the body) and histology (kind of cells affected and the way the cells behave). Specific types of cancer, as defined by site and histology, are often uncommon and many are rare. Each type of cancer has its own constellation of risk factors.

Because cancer is really many diseases, investigation of a reported cancer cluster starts with creating a case definition. For example, a general term like "leukemia" is not an appropriate case definition. There are many kinds of leukemia, each with unique age distributions and unique sets of known or suspected risk factors. The more specific the case definition, the more likely the cases are to have common risk factors. A precise case definition contributes to the possibility of discovering a risk factor because it focuses attention on a single disease process that may arise from a specific exposure.

Time Period

Cancer is complex and multifactorial (many factors interact) and develops over many years (latency period). With rare exceptions, no single event causes cancer and no single exposure or risk factor explains all cancers of a given type. Not all cases of cancer can be traced to specific exposures or risk factors. The causal process for all kinds of cancer includes multiple mutations of genetic material in a cell that result in disordered growth and function. Cells have a remarkable ability to repair mutations so multiple events over many years are usually required to cause cancer. Because of the complex causal pathways and the latency period, it is often difficult to identify events that contributed to cancer. As a preliminary step, an investigation of a potential cancer cluster might look at incidence before and after a suspected hazard was introduced into the environment.

Population at Risk

Because many potential cancer clusters are reported on the basis of suspected exposure to a local environmental hazard, the population at risk may initially be defined as people living near the hazard. However, some current residents may be newcomers and some previous residents may have left. Mobility makes it difficult to define the population at risk. The Montana Central Tumor Registry records the address at time of diagnosis for each cancer patient but that address may not reflect the true history of possible exposure. The population at risk may be refined to include only long-term residents of the area near a suspected hazard.

Excess Occurrence

Cancer occurs in all communities. The prevalence (number of cases that exist at any given time) and incidence (number of new cases diagnosed during a specified period of time) are described by either age-specific or age-adjusted rates, to take into account that cancer usually occurs in older individuals. Rates are expressed

using a common denominator, usually per 100,000 people at risk. Age-adjusted rates allow us to make accurate comparisons among communities and to judge whether there may be an unusually high incidence in a given community.

Many reported clusters are not verified so the process stops here. The most common reason a cluster is not verified is that the cases which prompted the report are diverse and do not fall into a single case definition. Another common reason a cluster is not verified is that cases have not lived in a community long enough for local conditions to have caused or contributed to their disease.

Three criteria are used to determine whether an investigation should occur:

1) three or more cases meet the case definition;
2) cases have a plausible common cause or share a common exposure; and
3) cases have lived in the area for an appropriate period of time for the common exposure to be related to their cancer.

Investigation: Because an investigation may require contacting patients or their families, it can be very distressing for those involved. An investigation is not undertaken unless there is persuasive evidence of a cancer cluster. If a cluster is verified, DPHHS initiates an investigation. All known risk factors are considered, including any environmental hazards that may have prompted the initial report. At this stage, DPHHS will contact health care providers of record, and possibly patients or their surviving relatives, to gather information on individual life histories, risk factors, and potential exposures to suspected hazards. If cases in the cluster cannot be explained by known risk factors, or if life histories point to a common exposure or environmental hazard, DPHHS will search for detailed information on the suspected hazard and its possible presence in the area. An epidemiologic study will be initiated if one or more of the following criteria is met:

1) an environmental hazard exists and is a biologically plausible risk for the type of cancer observed;
2) there is a high prevalence or sudden increase in cancer meeting the case definition in the area associated with the environmental hazard; or
3) there is no other explanation for the cancer cases and they share exposure to the environmental hazard.

Epidemiologic Study: If DPHHS determines that it is necessary to conduct an epidemiologic study, it will consult with specialists from appropriate agencies such as the Centers for Disease Control and Prevention, the Agency for Toxic Substances and Disease Registry, or the Environmental Protection Agency.

The Problem of Small Numbers

It is difficult to interpret incidence rates for small segments of a population such as Montana's counties. In effect, any single case of cancer might appear to be an excess. Although the occurrence of two or three cases can be very striking in a small population, it rarely indicates a cluster.

Incidence rates are computed as the number of cases divided by the number of people in the population at risk, multiplied by 100,000 to achieve a common denominator to compare rates. The table on the next page, based on data from the Montana Central Tumor Registry, shows the incidence of brain cancer in Montana and two counties, one of the larger and one of the smaller counties in the state. In 2000, five cases of brain cancer in the large county with a population of 55,716 yielded a crude (not age-adjusted) incidence rate of 9.0 per 100,000, compared the state as a whole with 73 cases and a population of more than 900,000, or a crude rate of 8.1 per 100,000. Assuming that the large county and the state have similar age distributions, it might appear that the county rate is higher than the state rate. However, if one of the five cases in the large county had been diagnosed a year earlier or later, the computed rate for 2000 would be 7.2 per 100,000, lower than the state rate. One way to deal with this variability is to use multiple year average incidence rates for comparison. The small county had only two cases of brain cancer in the five-year period, but both were diagnosed in the same year. The annual crude incidence rate was very high at 88.8 per 100,000 but the five-year average was substantially lower at 17.6 per 100,000.

It is also necessary to take into account the age structure of populations when comparing the incidence of cancer, which has a strong association with age. For example, the crude five-year average brain cancer incidence rate for Montana was 7.8 per 100,000, but when adjusted for the age distribution of the population it was 7.4 For the large county, the crude and age-adjusted rates were the same, 9.7 per 100,000. However, for the small county, the crude incidence rate was 17.6 while the age-adjusted rate was 11.2 per 100,000. The population of the small county was actually shrinking over the five-year period, and age-adjustment substantially reduced the incidence rate of cancer in this example, suggesting a reduced birth rate or out-migration of young adults and an overall aging of the county population.

Statistics based on small numbers of cases are unstable. This instability is measured by the Confidence Interval (CI) around the rate. For a 95% CI, the true cancer rate has a probability of 95% of falling within the range. For the large county, we are 95% sure that the true rate is between 5.7 and 13.7 per 100,000. The CI for the state rate, with a substantially larger population and more cases, is 6.4 to 8.4 per 100,000. Because the CI for the large county includes the state rate (5.7 to 13.7 includes 7.4), the rates are not considered statistically significantly different. Although the incidence rate for the small county appears to be substantially greater than the state rate, its CI is much larger, from 0 to 27.2, and not statistically different from the state rate.

Incidence of Brain Cancer in Montana and Two Counties

	Montana				Large County				Small County			
Year	cases	population	crude rate[3]	age-adjusted rate (CI)[4]	cases	population	crude rate	age-adjusted rate (CI)	cases	population	crude rate	age-adjusted rate (CI)
1999	60	882,779	6.8	6.6	3	54,075	5.6	5.3	2	2,253	88.8	52.8
2000	73	903,157	8.1	7.8	5	55,716	9.0	9.1	0	2,158	0	0
2001	62	904,433	6.9	6.7	4	56,094	7.1	6.9	0	2,096	0	0
2002	89	909,453	9.8	9.4	10	56,554	17.8	19.3	0	2,037	0	0
2003	67	917,621	7.3	6.9	5	57,137	8.8	8.5	0	2,055	0	0
Average	70		7.8	7.4 (6.4 - 8.4)	5.4		9.7	9.7 (5.7 - 13.7)	0.5		17.6	11.2 (0 - 27.2)

We would therefore conclude that, in spite of a striking incidence of two cases in a single year in the small county, there is no excess of brain cancer there. In fact, the two cases of brain cancer were of different histologic types. One is more common in males, the other more common in females. One has bimodal age peaks (under age 10 and over age 25), the other is rare before the teens and increases linearly with age. The two types have no known risk factors in common and an initial review of cases would have placed them in different case definitions.

Cancer is becoming more common as the population ages and other causes of morbidity and mortality are brought under control. True cancer clusters are extremely rare, as are clearly identifiable environmental causes of cancer. The Montana Cancer Control Section of DPHHS uses the MCTR to monitor cancer trends in the state and to respond to public inquiries.

[3] per 100,000 total population
[4] per 100,000 population age-adjusted to the 2000 Census population; CI = 95% Confidence Interval around the point estimate

Please visit our website at www.cancer.mt.gov

For more information about the **Montana Cancer Control Program** contact Ginny Furshong, Program Manager, 406-444-6888, gfurshong@mt.gov

For more information about the **Montana Breast and Cervical Health Program**, contact Karan Kunz, Program Manager, 4060444-0063, kkunz@mt.gov

For more information about the **Montana Central Tumor Registry**, contact Debbi Lemons, Program Manager, 406-444-2618, dlemons@mt.gov

For more information about **cancer data and analysis**, contact Carol Ballew, PhD, Epidemiologist, 406-444-6988, cballew@mt.gov

3,000 copies of this document were produced at a cost of $0.75 per copy, for a total cost of $2250.00 for printing and $0 for distribution.

Alternative formats of this document will be provided upon request. Please contact Dr. Ballew at 406-444-6988 or cballew@mt.gov.

Montana Cancer Control Section
Montana Department of Health and Human Services
1400 Broadway C-317, PO Box 202951
Helena, MT 59620-2951